Claim 9 is also allowable and Claims 8 and 10-14 are submitted to be allowable because the standard of undue experimentation is not applicable here.

35 U.S.C. 112, first paragraph, is reproduced below.

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As indicated above, 35 U.S.C. 112 requires a description enabling a skilled person to make and use. In this case, there is not question of how to make--only a question of how to use. For this case, In re Hitchings, 144 U.S.P.Q. 637 (C.C.P.A. 1965) indicates an express disclosure of manner of administration and dosage, will satisfy the how to use requirement. Dosage and route of administration are clearly set forth at page 21 in the application as filed and are exemplified in Examples XV-XXV at pages 40-42 of the application as filed. Thus, the how to use requirement is clearly met.

The rejection here is clearly one for lack of utility, masquerading as a rejection under 35 U.S.C. 112. Thus, the utility guidelines of the USPTO (MPEP Section 2107) rather than the undue experimentation factors, apply. The utility guidelines cannot be avoided by bringing the rejection under 35 U.S.C. 112, first paragraph, rather than under 35 U.S.C. 101. See MPEP Section 2164.07 and In re Brana, 34 U.S.P.Q. 2d1 436 (Fed. Cir. 1995).

Rejections for lack of utility have to do with burdens. Initially, the burden is on the examiner to show that one of ordinary skill in the art would reasonably doubt the asserted utility. See MPEP Section 2164.07 (I)(B). The examiner has tried to meet this burden by citing Dermer (1994), which generally demeans reliance on cell line data for *in vivo* cancer utility.

Dermer is submitted to be defective for the purpose on which it is relied.

Firstly, this is because there is a Commissioner's Decision which indicates that reliance on Dermer would be misplaced. In this regard, see In re Hozumi, 226 U.S.P.Q. 353 (Comm Dec. 1985). Hozumi holds that cell line data for human myelocytic leukemia cells HL-60 is sufficient for *in vivo* treatment claims in respect to leukemia and suggests that cell line data for solid tumor cell lines wold be sufficient for claims in respect to treatment of solid tumors. The instant case meets the Commissioner's Decision test for lymphoma/leukemia treatment and for solid tumor treatment. Background Example 1 at pages 32 and 33 of the application as filed, provides data on a human acute monocytic leukemia cell line (THP-1) as well as on the solid tumor cell lines HeLa (derived from adenocarcinoma of the cervix) and A549 (derived from liver carcinomatous tissue). Thus Hozumi indicates there is sufficient data here for *in vivo* utility. Hozumi has not been withdrawn or reversed despite Dermer (1994). Use of human cancer cell lines is still standard operating procedure, for cancer research. The PTO is still granting patents where the only evidence of *in vivo* anti-cancer utility is cell line data . See Dannenberg et al U.S. Patent No. 6,291,490.

Secondly, Dermer is submitted to be defective because Dermer is making a general assertion. Rather the PTO needs to cast doubt on the specific usefulness in this case. For example, the PTO needs to show that the specific cell lines used here do not mimic the human body. Or the PTO needs to cast doubt on the specific usefulness of some specific treating agent set forth in the application. See In re Brana, 34 U.S.P.Q. 2d 1436, 1441 (Fed. Cir. 1995).

Thirdly, Dermer is submitted to be defective because cells that Dermer mentions are much different from the cell lines tested in the instant patent application. Dermer discusses 3T3 cells. 3T3 cells are embryonic fibroblast cell lines derived from Swiss mice, used for transfection studies

with a DNA virus. This is much different from the case here where cell lines obtained from human cancer cells, and representing actual human leukemia/lymphoma and tumors, are used to determine the presence of an enzyme activity to understand a mechanism for *in vivo* treatment of cancer.

Fourthly, the rejection is defective because the action has not shown that the Dermer thesis is generally accepted by the scientific community. The Dermer citation is one researcher's opinion and is clearly controversial. Consider the following statement by a review of Dermer's book which presents the same thesis.

> The book does have its limitations. Dermer apparently wrote this partly to inform the public, partly to level some scores in his profession. He is less successful at presenting another model for research than in explaining the shortcoming of current cellular research. He suggests animal research but fails to review the logical results of that theory. Instead of testing cells in the laboratory, will we experiment on millions of beagles? Ultimately the book is limited because the author fails to thoroughly explore his own theories.

Dermer's thesis is recognized as limited and therefore insufficient to support the rejection.

Aside from the above, data on cell lines plus past history is indicated in Brana to be sufficient for *in vivo* cancer treatment utility. The instant case meets this text.

Data in this application shows the GS-FDH enzyme activity is conserved in all cells tested, namely *E. coli* strain RK4936, mouse macrophage RAW264.7 cells, mouse SVEC4-10 endothelial cells, mouse SE4OLT-SMC smooth muscle cells, human HeLa, A549, and THP-1 cell lines, wild-type Y190 yeast cells, hepatocytes of wild-type mice and in liver tissues from wild-type mice. Moreover, GS-FDH activity has shown in three diverse human cancer cell lines which are submitted to be sufficiently representative of all mammalian cancer cells. The presence of the enzyme is submitted to show the presence of nitrosoglutathione (GSNO) which has been

discovered in making the invention to metabolize GSNO and to be the best substrate for the enzyme. GSNO is accepted from past history to inhibit the growth of pathologically proliferating mammalian cells *in vivo*. See U.S. Patent No. 6,057,367. Thus, the inhibition of the enzyme which metabolizes GSNO would be expected to inhibit pathologically proliferating cells. The principle that inhibition of the GS-FDH enzyme in cells will increase the effect of GSNO where GSNO activity is therapeutic, is verified by testing on cells from pathological tissue. See page 36 of the application as filed. In other words, cell data is shown to translate to inhibition of GSNO *in vivo*. It is submitted that this confirms the applicability of the invention to inhibiting the proliferation of pathologically proliferating cells *in vivo*. Cell line data plus past history is present, and this test of Brana is met.

Note that the court in Brana explicitly said:

> "The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions...."

Indeed, the court said that the PTO had confused the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a drug. Brana thus makes clear, if it had not been clear before, that a specific pharmaceutical utility allegation is sufficient without detailed proof that a drug would ultimately be useful in human treatment.

Allowance is requested.

Respectfully submitted,

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